The Gulf War Illness Landscape

The 1990-91 Gulf War

The 1990-91 Persian Gulf War was an international conflict in response to Iraq's invasion and annexation of Kuwait. In anticipation of a conflict to liberate Kuwait, the U.S. and an allied Coalition of 34 nations began a military buildup codenamed Operation Desert Shield. The Coalition included the U.S., The UK, France and Saudi Arabia, among other nations. The buildup was begun by the U.S. and Saudi Arabia in August 1990 and continued through January 1991 at which time Coalition troops at the ready numbered 750,000 and included 540,000 U.S. personnel.

The Southwest Asia theater of operations is generally defined as the area that includes the Persian Gulf, Red Sea, Gulf of Oman, Gulf of Aden, that portion of the Arabian Sea that lies north of 10 degrees N. latitude and west of 68 degrees E. longitude, as well as the total land areas of Iraq, Kuwait, Saudi Arabia, Oman, Bahrain, Qatar, and United Arab Emirates.

Coalition attacks on Iraqi forces began with a massive six-week air and naval bombardment campaign on January 17, 1991, aimed at targets within Iraq. In response, Saddam Hussein launched Scud missiles at targets within Israel, Saudi Arabia, Bahrain, and Qatar. This combat phase was codenamed Operation Desert Storm.

The bombardment phase was followed by a ground assault on February 23, 1991. The ground assault was codenamed Operation Desert Sabre, but it is often referred to as a second phase of Operation Desert Storm. U.S. troops engaged in heavy battles against the Iraqi forces, including fierce tank battles and breaching minefields. As Coalition forces advanced into Kuwait, many of the remaining Iraqi troops there surrendered to Coalition forces. Others set fire to 600-700 oil wells in Kuwait as they retreated into Iraq.

Coalition forces also advanced into Iraq through the western frontier with Saudi Arabia, outflanking and encircling the retreating Iraqi military. The outcome was a decisive victory for the Coalition forces. By the time that President George H.W. Bush declared a cease-fire to the Gulf War (GW) on February 28, 1991, most Iraqi forces in Kuwait had either surrendered or fled. By July 1991, the last U.S. troops who had participated in the ground war returned home. U.S. forces experienced 147 casualties on the battlefield and an additional 145 personnel were killed by non-battle related causes.

Gulf War Illness Primary Features, Prevalence and Prognosis

Symptoms of Gulf War Illness

Within a short time after the 1990-91 GW, Veterans who served in and around the theater of operations developed enduring chronic, unexplained conditions and/or constellations of symptoms and illnesses that could not be explained by established medical diagnoses, psychiatric diagnoses, or standard laboratory tests.

Symptoms experienced and reported by GW Veterans vary widely. However, the multitude of symptoms reported are of a similar clinical description in the many groups studied and usually include some combination of widespread pain, muscle aches, headache, persistent problems with memory and thinking, fatigue, breathing problems, stomach and intestinal symptoms, and skin abnormalities. In addition to the physical issues involved, changes in behavior and problems with interpersonal relationships also frequently occur.

Initially, this constellation of disorders was referred to as the "Gulf War Syndrome". Other names given to these problems included chronic multi-symptom illness (CMI), undiagnosed illness, Gulf War Illness (GWI), and other terms. Currently, "Gulf War illness" is the term recommended by the National Academy of Medicine (formerly the Institute of Medicine or IOM) and is most commonly used by scientists, clinicians, Veterans organizations and the U.S. Department of Defense (DoD).

Prevalence

GWI is estimated to have affected 175,000 to 250,000 of the nearly 700,000 troops deployed to the 1990-91 GW theater of operations. Twenty-seven of the twenty-eight Coalition members participating in the GW conflict have reported GWI in their troops. Epidemiologic studies indicate that rates of GWI vary in different subgroups of GW Veterans. GWI affects Veterans who served in the U.S. Army and Marines Corps at higher rates than those that served in the Navy and Air Force, and U.S. enlisted personnel are affected more than officers. Studies also indicate that GWI rates differ according to where Veterans were located during deployment, with the highest rates among troops who served in forward areas.

Prognosis

The 2014 report by the Department of Veterans Affairs (VA) Research Advisory Committee on Gulf War Veterans' Illnesses (RAC) summarized investigations addressing health changes related to GWI (RACGWVI, 2014 pp. 21-22). The report states that Veterans of the 1990-91 GW generally are in poorer health and present with greater disability than other Veterans of the same era that were not deployed to the Persian Gulf. Research suggests that the GWI symptomology experienced by Veterans has not improved over the last 25 years with few experiencing improvement or recovery. It is expected that many GW Veterans will soon begin to experience the common co-morbidities associated with aging. The effect that aging will have on this unique and vulnerable population remains a matter of significant concern and population-based research to obtain a better understanding of mortality, morbidity, and symptomology over time is needed. Further description and consideration of distinct GWI subpopulations defined by exposure history, location in theatre or demographic is also important.

Etiology of Gulf War Illness

During the GW, Service members were exposed to low levels of chemicals including chemical warfare agents released by the destruction of Iraqi facilities, widespread spraying and use of pesticides, prophylactic medications to protect against hazardous exposures, constant dust and sand storms, and effluent from oil well fires ignited by Iraqi troops. Uncertainties regarding type and dose of agent exposure(s), and a lack of scientific knowledge about the synergistic effects of combined agent exposures have precluded a consistent theory of GWI etiology. There remains a need to identify objective markers of GW-relevant exposures and downstream effects of those exposures, including latent effects that represent the current status of GWI patients.

GW-Relevant Exposures

Cholinergic agents represent the most likely class of exposures to the broadest fraction of the Service members deployed to the GW. Of these, the organophosphates comprising the chemical warfare agents sarin, cyclosarin, soman, and the pesticides permethrin (PER) and chlorpyrifos (CPF) have received considerable attention. Other cholinergic agents include pyridostigmine bromide (PB) pills given as a prophylaxis against nerve agents and the insect repellant N,N-diethyl-meta-toluamide (DEET). Virtually all deployed troops were exposed to the pesticide PER used on clothing to kill insects, the area pesticide CPF used in no-pest strips in mess and residential areas, and the insect repellant DEET applied directly to skin. Many troops were given PB pills to take in anticipation of a nerve agent attack and many troops are likely to have been exposed to vapor plumes resulting from destruction of chemical weapons including sarin, cyclosarin, and possibly mustard gas and soman.

Exposures to other possible etiologic agents include airborne particulates and emissions from Kuwaiti oil well fires, desert dust, multiple vaccinations (including anthrax vaccination), depleted uranium (DU), chemical resistant coating (CARC) paint, psychological and physiological stress, heat, and miscellaneous petroleum products such as cleaners, lubricants, and fuels.

It is generally assumed that individuals meeting the criteria for GWI were likely exposed to multiple agents. Therefore, further investigations using methods that consider a combination of exposures are essential.

GW-Relevant Animal Models

Several animal models have been developed to elucidate possible molecular and physiological mechanisms underlying GWI. These models have been used to characterize molecular, cellular, and functional effects associated with chemical exposures similar to those encountered by Veterans during the GW. These studies have provided evidence for brain, autonomic, behavioral, neuroendocrine, immune, and epigenetic effects that were previously unknown.

White et al. have summarized a number of rat and mouse studies evaluating the effects of exposures to combinations of PB, PER, CPF, sarin, diisopropyl fluorophosphates (DFP, a sarin surrogate), and stress, usually at dosage levels that do not produce overt symptoms of toxicity (White, 2016 pp. 16-18). Beginning with work of Abou Donia and colleagues with a rat model of PB, DEET and CPF exposures (Abou-Donia, 1996), these models have been shown to recreate GWI-like symptoms. Furthermore, these studies have shown that the absorption, metabolism, and biological function following exposure to a combination of chemicals are different than the absorption, metabolism, and biological function of the individual exposures when studied separately (RACGWI, 2008). The findings obtained with several rodent GWI models are described below; however, this is not a comprehensive list of GWI models. Animal model development that has been supported by the DoD Gulf War Illness Research Program (GWIRP) can be found at (http://cdmrp.army.mil/gwirp/resources/gwirpresources).

Several investigators have exposed rodents to a combination of PB, PER, DEET, and restraint stress in doses that do not give rise to immediately apparent toxic effects. Such treatment was reported to result in depressive behavior, lack of motivation, and memory defects (Hattiangady, 2014), (Parihar, 2013) to induce abnormal lipid metabolism and increase immune signaling (Abdullah, 2012) and to induce long-term epigenetic alterations (Pierce, 2016). Other rodent models have shown various types of delayed central nervous system (CNS) abnormalities that appear sometime after exposures to combinations of CPF with DEET or PB or PB plus PER (Nutter, 2105), (Cooper, 2016), (Torres-Altoro, 2011), (Ojo, 2014).

Evidence of CNS inflammation was reported early on (Bozkurt, 2010) and has been the subject of extensive research recently. A series of studies has established a model based on dual exposure to PB and PER. Using this model, researchers have documented neurobehavioral, neuropathological, and neuroinflammatory effects after PB plus PER exposure in the short, mid, and long term. Genomic and proteomic studies were used to discern many features of the neuroinflammatory effect (Abdullah, 2011), (Abdullah, 2013), (Zakirova, 2015), and (Zakirova, 2016).

O'Callaghan et al. recently reported very compelling results using only a single chemical agent (O'Callaghan, 2015); however, this exposure was preceded by pretreatment with corticosterone (CORT), a stress hormone that would normally be expected to quell inflammatory responses produced by external stressors. Exposure to a single dose of the acetylcholinesterase inhibitor DFP was found to result in inflammation in the brain, but pretreatment with CORT was found to exacerbate the CNS inflammatory response to DFP and to produce a persistent "priming" of the immune system to continue to generate exacerbated responses to subsequent irritant challenges. The priming can be maintained for months in the mouse model (equivalent of 20 years in humans) by periodic low dosing with CORT. This model and variants of it, including one that will employ sarin, are currently being used and expanded in research being carried out by two research consortia funded by the GWIRP to identify new features of GWI pathobiology and new targets for treatment (Morris, FY 2012) (Sullivan, FY 2012).

Other studies have focused on additional cellular and subcellular targets of GW chemical agents and suggest abnormalities associated with cholinesterases, tubulin (Grigoryan, 2008), (Jiang, 2010) (Grigoryan, 2009), impaired axonal transport and mitochondrial dysfunction (Middlemore-Risher, 2011). Microtubule dysfunction is currently being studied in vitro under one of the GWIRP consortium awards (Sullivan, FY 2012), and mitochondrial defects are the target of at least one experimental treatment approach (Golomb, 2014).

Further studies that characterize and refine the chronic effects of neurotoxic exposures at dosages comparable to that encountered in-theatre in established models of GWI are needed.

Pathobiology of Gulf War Illness

Because exposures to various neurotoxicants were known to occur in the GW and many of the symptoms of GWI clearly relate to nervous system dysfunction, much GWI research has focused on pathobiology of the nervous system. Other areas that have been and are actively being investigated include the immune/inflammatory and gastrointestinal systems and molecular systems for respiration and management of oxidative potential. From studies that have included female GW Veterans, it is apparent that gender differences may play a role in the underlying pathobiology of GWI; however, further research into gender and racial differences is needed.

Imaging Studies

Consistent differences between GWI cases and controls have been demonstrated using various brain imaging technologies to measure brain structure and function.

Structural magnetic resonance imaging techniques have been employed in GW Veteran populations to determine structural changes in the brain, such as a reduction in brain size due to specific exposures in theater or changes occurring after GWI diagnosis. MRI-based measurements of specific brain areas and their volumes (segmentation and volumetry techniques) have revealed frank reductions of white and gray matter volumes in Veterans with suspected sarin/cyclosarin-exposure when compared to controls (Chao, 2010) (Chao, 2011) (Chao, 2014). Using Diffusion Tensor Imaging (DTI), which assesses the integrity and connectivity of white matter structures to other parts of the brain, Rayhan and Stevens reported increased axial diffusivity in subjects with GWI compared to controls. These results suggest that the white matter in GWI patients functions less effectively. Furthermore, they reported that increased diffusivity seen in the GWI patients was associated with increased fatigue, pain, and hyperalgesia (Rayhan, 2013a). Chao et al. also observed increased axial diffusivity in GWI patients and found that the increased diffusivity correlated with poorer neurobehavioral performance (Chao, 2015). In functional MRI (fMRI) studies, where activation of brain structures in response to cognitive and other behavioral challenges can be visualized, Calley et al. report case/control differences in specific brain regions during a Semantic Object Retrieval Test (Calley, 2010).

fMRI studies using a pre/post-exercise protocol showed that brain regions activated in response to innocuous heat stimulus following exercise were different among Veterans diagnosed with the three subtypes of GWI defined by the Haley criteria (Haley, 2001) and that as a whole, the GWI group had distinct responses post-exercise when compared to the control group (Gopinath, 2012). Furthermore, the Haley-defined GWI subgroups showed atrophy in different brain regions and exhibited compensation in different brain regions during a verbal working memory task following exercise. Another MRI study revealed case/control differences in regional brain activation during memory encoding and memory recall (Hubbard, 2013).

Neurocognitive Findings

Because the neurocognitive and affective symptoms reported by GW Veterans commonly include problems in memory, concentration, and mood, psychological tests are often used to quantify neurobehavioral function in this Veteran group.

A large study comparing deployed GW Veterans versus non-deployed era Veterans found that deployed participants performed worse than their non-deployed counterparts on tests that assess short-term memory attention, visuospatial abilities, executive function, and fine motor coordination and speed (Toomey, 2009). Differences in performance on specific cognitive tasks were associated with self-reported exposures to specific chemical agents in theater. Self-reported exposure was found to predict poorer performance outcomes on measures of short-term memory, attention, and affective functions (White, 2001), and to be associated with poorer executive function and greater mood complaints (Sullivan, 2003). In a number of studies, researchers reported poorer visuo-spatial, and memory functions, and greater dysphoria in Veterans meeting the criteria for GWI versus controls (Anger, 1999), (Axelrod, 1997), (Binder, 1999), (Bunegin, 2001), (Lange, 2001), (Storzbach, 2001), (Storzbach, 2000), (Odegard, 2013) (Sullivan, 2003). One study showed little difference between cases and controls in cognitive domains but did find significantly poorer reports of mood and quality of life in those with GWI (Wallin, 2009); this study involved a very small sample of GW-deployed veterans and lacked the statistical power to detect subtle but significant differences in cognitive outcomes.

Autonomic and Neuroendocrine Systems

Studies have linked autonomic dysregulation to symptoms experienced by GW Veterans. In these studies, important differences in function between ill GW Veterans, controls and among Veterans with differing Haley syndromes are not apparent during resting or work but rather emerge following some type of physiological challenge. The challenge used in these studies is most often physical exercise, but can take other forms. In animal models pharmacological challenges have been used (e.g., drugs that increase heart rate). Studies in the GWI literature referring to pre- and post- challenge testing most often refer to testing before and after such a challenge (or during peak effort) and not to testing before and after chemical exposure as is often the case in many toxicological studies.

Tests of parasympathetic and sympathetic nervous system regulation in GW Veterans have demonstrated that some symptoms, such as chronic diarrhea, dizziness, fatigue, as well as changes in cardiovascular indices, may be due to subtle autonomic system dysfunction (Haley, 2004), (Rayhan, 2013b).

Due to the extreme conditions of deployment and possible exposure to pathogenic agents during the GW, it has been suggested that the neuroendocrine control system may have been pushed beyond its normal operating capacity. Thus, neuroendocrine dysregulation as a result of GW deployment has been reported, including demonstrations of pronounced differences between GWI Veteran and controls after exercise and other challenges. Specific patterns of altered hypothalamic-pituitary-adrenal (HPA) axis functioning that are distinct from other conditions such as PTSD have been identified (Ben-Zvi, 2009), (Golier, 2007), (Golier, 2009). A GWIRP-funded project (Craddock, 2014) found that regulation of sex hormones, through the hypothalamic-pituitary-gonad (HPG) axis and components of innate and adaptive immunity undergo distinct and significant remodeling following exercise challenges in Veterans with GWI (Broderick, 2011).

Further investigation into altered regulation of these systems is ongoing. Research under a GWIRP-supported consortium (Morris, FY 2012) integrates basic and clinical research to identify the metabolic signaling mechanisms involved in the disruption of autonomic cardiovascular function and endocrine functions in GWI.

Immune System

Evidence from various fields has demonstrated multiple channels of communication between the brain and the immune system and brain-immune inter-relationships have been investigated in GWI. In the short term, inflammatory responses generated by the immune system are helpful and elicit self-preserving physical responses; however, chronic inflammation can be maladaptive. This observation led to recent interest in neuroinflammatory chronic glial activation as a potential cause of chronic symptoms in GWI. Chronic glial activation results in the synthesis and release of pro-inflammatory cytokines and chemokines (O'Callaghan, 2008) and is particularly relevant to GWI because the effects are seen in both gray and white brain matter. Gray and white matter volumes have both been shown to be reduced in neurotoxicant-exposed and symptomatic GW Veterans (see Brain Imaging Studies above). In addition to lower white matter volumes, studies have shown reduced information processing speeds in symptomatic GW Veterans exposed to low-dose sarin, a neurotoxicant (Proctor, 2006). Taken together, the findings of reduced white matter volumes and poorer information processing suggest that glial cells may have an important role in the development and ongoing health symptoms and cognitive complaints of GW Veterans. A GWIRP-funded project (Klimas, FY 2008) used comprehensive molecular profiling combined with control theory to link a stress-potentiated neuro-inflammatory response with symptom severity via changes in immune cell abundance, function, and signaling (Broderick, 2013).

Further investigation into whether GWI is related to chronic brain-immune activation and inflammation is ongoing under a GWIRP-supported consortium (Sullivan, 2012).

Mitochondrial Dysfunction

Exposures linked to GWI are known to impair cell energy, and adverse cell energetics has been shown to contribute to symptoms consistent with GWI. Given these observations and because the mitochondrion is the source of chemical energy for the cell, the potential relationship between mitochondrial dysfunction and GWI has been subject to investigation. A GWIRP-funded study recently provided the first objective evidence of mitochondrial dysfunction in Veterans with GWI. Compared to controls, Veterans with GWI exhibited prolonged postexercise recovery of phosphocreatine, a compound used as a backup energy store and a robust index of mitochondrial function (Koslik, 2014). This finding supports the presence of mitochondrial pathology in GWI.

Continued research focusing on the central and autonomic nervous systems and on neuroendocrine, immunological, and mitochondrial outcomes is required in order to identify treatment targets and primary outcome targets to be improved during such treatments.

A biorepository effort and published pathobiological biomarker studies supported by the GWIRP to date can be found at http://cdmrp.army.mil/gwirp/resources/gwirpresources.

Gulf War Illness Case Definitions

Research on GWI has relied on a number of differing definitions of the disorder, including chronic multi-symptom illness (CMI) (Fukuda, 1998), the Kansas GWI definition (Steele, 2000), the Haley syndrome criteria (Haley, 1997), (Haley, 2001), and adaptations of these approaches.

An IOM panel recommended the use of the CMI definition in clinical settings as it is somewhat inclusive (IOM, 2014). In the same report, the panel also recommended use of the Kansas definition in research settings because it is more selective and includes various exclusionary criteria. Current best practice in research is to use of one of the two IOM-recommended case definitions (CMI or Kansas) for primary analyses that best fit the current study and also include the criteria that will allow use of the other definition to facilitate cross-comparison of study results. For example, a study of GW populations might categorize participants primarily according to the Kansas definition but then further categorize them according to the CMI definition to allow comparisons to prior studies that have used each definition.

In the absence of a consensus, the need continues for applied research aimed at producing a robust, evidence-based case definition for both clinical and research applications.

The CMI Definition (A.K.A. Fukuda or CDC definition)

The CMI case definition was developed by the U.S. Centers for Disease Control and Prevention (CDC) and was derived from clinical data and statistical analyses (Fukuda, 1998). The investigators conducted a cross-sectional survey in a Pennsylvania-based Air National Guard unit and three comparison Air Force units.

The CMI definition is variously referred to in the literature as the CMI definition, the CDC definition (after the primary author's home institution) and the Fukuda definition (after the primary author). CMI is the most commonly used GWI case definition in epidemiologic research to date and is somewhat inclusive. In the primary publication describing the definition, the prevalence of GWI in deployed Veterans ran as high as 45% using the CMI criteria. The VA RAC estimated use of this definition to yield a prevalence as high as about 32% in the population of GW Veterans.

This analytic approach included a principal-components analysis of symptoms of fatigue, difficulty remembering or concentrating, moodiness, difficulty sleeping, and joint pain or stiffness followed by a confirmatory factor analysis. The definition thus requires more than one chronic (≥6 months) symptom in at least two of three categories: fatigue, mood and cognition, and musculoskeletal. It also allows sub-classification by severity; cases are considered severe when at least one symptom in each of the required categories is rated as severe. Risk factors associated with CMI were deployment to the GW, rank, age, being female, and smoking; cases also reported reduced functioning.

The Kansas Definition

The name of the Kansas definition reflects the origin of the Veteran group participating in the study that formulated the criteria for this definition of GWI. In the primary publication describing the definition, the prevalence of GWI in deployed Veterans ran as high as 34%. The VA RAC estimated that using the Kansas criteria to define GWI yields a prevalence in the range of 25% in deployed GW Veterans.

The definition was conceived when the Kansas Persian Gulf Veterans Health Initiative sponsored a study of deployment-related symptoms in 1998 (Steele, 2000). The investigators chose to develop a clinically based descriptive definition using correlated symptoms. Subjects were GW

Veterans (2,030) living in Kansas who participated in a telephone interview. The researchers developed a case definition that required: (1) Symptom onset after 1990; (2) Presence of symptoms in the year before the interview; (3) No diagnoses or treatment for exclusionary conditions (cancer, diabetes, heart disease, chronic infectious disease, lupus, multiple sclerosis, stroke, or any serious psychiatric condition); (4) Symptoms in at least three of six symptom groups: fatigue and sleep problems, pain, neurologic and mood, gastrointestinal, respiratory, and skin symptoms; (5) At least one moderately severe symptom or two or more symptoms within a symptom group. The Kansas study found GWI to be more prevalent in those GW Veterans who were women, who had lower income, those with less education, those who served in the U.S. Army, and those who served as enlisted personnel.

The Haley Definition

A third system for defining GWI was developed by Haley et al (Haley, 1997). This case definition includes three distinct syndrome complexes that distinguish correlated clusters of GWI symptoms. Haley and colleagues employed factor analytic techniques from standardized questionnaires to evaluate symptom data from a Seabees unit, with 249 of the 606 members across five southeastern states participating. Because the original study lacked a comparison group, syndrome criteria were later validated against an independent cohort of Veterans in north Texas (Haley, 2001). The study initially defined six potential syndromes, but three primary syndromes emerged: S*yndrome 1* (impaired cognition) is characterized by problems with attention, memory, and sleep along with depression; *Syndrome 2* (confusion/ataxia) includes problems with thinking and cognitive processing and balance and coordination; and *Syndrome 3* (neuropathic pain), is defined primarily by joint and muscle pain. The clinical definition originally proposed by Haley et al captured 34% of the cohort, while the six initial factor-derived syndromes collectively identified 25% of the veterans.

Lack of Standard Treatments

Clinical trials with the potential to have significant impact on the health and lives of Veterans with GWI continue to be an ongoing priority. In the absence of treatments specific for GWI, Veterans have tried a myriad of drugs and therapies to treat their varied symptoms. A primary focus of the GWIRP has been to fund research studies that test treatments for GWI and identify treatment targets. While most of these studies remain in progress, several have already shown varying levels of promise as GWI treatments.

Many Veterans suffering from GWI have sought out complementary/alternative therapies and holistic medicines for relief. Physical modalities (massage, sauna, physical therapy), lifestyle changes (diet change, exercise, avoidance of triggers), herbs, vitamins and nutritional supplements, alternative medicine practices (including but not limited to chiropractic modalities, acupuncture) and unconventional practices (Hubbard detoxification, hyperbaric oxygen therapy, chelation) have all been attempted by GW Veterans trying to ease their pain and other symptoms.

Ongoing trials of pharmaceutical interventions include re-purposing FDA-approved compounds targeting the major symptoms of GWI and/or are based on therapeutic targets identified in model systems. More treatment approaches based on known mechanistic pathways are needed, including a clear definition of clinical targets and defined clinical outcomes. The number of treatment studies has dramatically increased in recent years; however, only a limited number of trials have published results to date.

Published Results

The earliest federally funded multi-center clinical trials were VA and DoD funded trials that focused on antibiotic treatment (doxycycline) (Donta, 2004) and cognitive behavioral therapy with exercise (Donta, 2003). Neither intervention provided long-lasting improvement for a substantial number of Veterans.

Preliminary analysis from a placebo-controlled trial showed that 100mg of Coenzyme Q10 (known as CoQ10 or Ubiquinone) significantly improved general self-reported health, physical functioning, and among 20 symptoms each present in at least half the study participants, with the exception of sleep. These improvements included reducing commonly reported symptoms of fatigue, dysphoric mood, and pain (Golomb, 2014). These results are currently being expanded in a GWIRP-funded trial of a “mitochondrial cocktail” for GWI of CoQ10 plus a number of nutrients chosen to support cellular energy production and defend against oxidative stress and in a VA-sponsored trial of Ubiquinol, the reduced form of CoQ10.

In a randomized, sham controlled VA-funded trial of a nasal continuous positive airway pressure (CPAP) mask (Amin, 2011a), symptomatic GW Veterans with sleep-disordered breathing receiving the CPAP therapy showed significant improvements in fatigue scores, cognitive function, sleep quality, and measures of physical and mental health (Amin, 2011b).

Preliminary data from a GWIRP-funded acupuncture treatment study show that Veterans reported significant reductions in pain and both primary and secondary health complaints, with results being more positive in the bi-weekly versus weekly treatment group (Conboy, 2012). Current studies funded by the GWIRP and the VA are also investigating yoga as a treatment for GWI.

An amino acid supplement containing L-carnosine was found to reduce Irritable Bowel Syndrome (IBS)-associated diarrhea in a randomized, controlled GWIRP-funded trial in GW Veterans (Baraniuk, 2013). Veterans receiving L-carnosine showed a significant improvement in performance in a cognitive task but no improvement in fatigue, pain, hyperalgesia, or activity levels.

Results from a 26-week GWIRP-funded trial comparing standard care to nasal irrigation with either saline or a xylitol solution revealed both irrigation protocols reduced GWI respiratory (chronic rhinosinusitis) and fatigue symptoms (Hayer, 2015).

Administration of the glucocorticoid receptor antagonist mifepristone to GW Veterans in a GWIRP-funded randomized trial resulted in an improvement in verbal learning but no improvement in self-reported physical health or in other self-reported measures of mental health (Golier, 2016).

Ongoing Intervention Studies

The GWIRP is currently funding many early phase clinical trials aimed at GWI. Interventions include direct electrical nerve stimulation, re-purposing FDA-approved pharmaceuticals, and dietary protocols and/or nutraceuticals. Both ongoing and closed GWIRP-supported clinical treatment trials and pilot studies can be found at http://cdmrp.army.mil/gwirp/resources/cinterventions

References:

Abdullah L, Crynen G, Reed J, Bishop A, Phillips J, Ferguson S, et al. 2011. Proteomic CNS profile of delayed cognitive impairment in mice exposed to Gulf War agents. *Neuromolecular Medicine, 13*(4), 275-288.

Abdullah L, Evans JE, Bishop A, Reed JM, Crynen G, Phillips J, et al. 2012. Lipidomic profiling of phosphocholine-containing brain lipids in mice with sensorimotor deficits and anxiety-like features after exposure to Gulf War agents. *Neuromolecular Medicine, 14*(4), 349-361.

Abdullah L, Evans JE, Montague H, Reed JM, Moser A, Crynen G, et al. 2013. Chronic elevation of phosphocholine containing lipids in mice exposed to Gulf War agents pyridostigmine bromide and permethrin. *Neurotoxicology and Teratology, 40*, 74-84.

Abou-Donia MB, Wilmarth KR, Abdel-Rahman AA, Jensen KF, Oehme FW, and Kurt TL. 1996. Neurotoxicity resulting from coexposure to pyridostigmine bromide, deet, and permethrin: implications of Gulf War chemical exposures. *Journal of Toxicology and Environmental Health, 48*(1), 35-56.

Amin MM, Belisova Z, Hossain S, Gold MS, Broderick JE, and Gold AR. 2011b. Inspiratory airflow dynamics during sleep in veterans with Gulf War illness: a controlled study. *Sleep and Breathing, 15*(3), 333-339.

Amin MM, Gold MS, Broderick JE, and Gold AR. 2011a. The effect of nasal continuous positive airway pressure on the symptoms of Gulf War illness. *Sleep and Breathing, 15*(3), 579-587.

Anger WK, Storzbach D, Binder LM, Campbell KA, Rohlman DS, McCauley L, et al. 1999. Neurobehavioral deficits in Persian Gulf veterans: evidence from a population-based study. Portland Environmental Hazards Research Center. *Journal of the International Neuropsychological Society, 5*(3), 203-212.

Axelrod BN and Milner IB. 1997. Neuropsychological findings in a sample of Operation Desert Storm veterans. *The Journal of Neuropsychiatry and Clinical Neurosciences, 9*(1), 23-28.

Baraniuk JN, El-Amin S, Corey R, Rayhan R, and Timbol C. 2013. Carnosine treatment for gulf war illness: a randomized controlled trial. *Global Journal of Health Science, 5*(3), 69-81.

Ben-Zvi A, Vernon SD, and Broderick G. 2009. Model-based therapeutic correction of hypothalamic-pituitary-adrenal axis dysfunction. *PLoS Computational Biology, 5*(1), e1000273.

Binder LM, Storzbach D, Anger WK, Campbell KA, and Rohlman DS. 1999. Subjective cognitive complaints, affective distress, and objective cognitive performance in Persian Gulf War veterans. *Archives of Clinical Neuropsychology, 14*(6), 531-536.

Bozkurt A, Yardan T, Ciftcioglu E, Baydin A, Hakligor A, Bitigic M, et al. 2010. Time course of serum S100B protein and neuron-specific enolase levels of a single dose of chlorpyrifos in rats. *Basic and Clinical Pharmacology and Toxicology, 107*(5), 893-898.

Broderick G, Ben-Hamo R, Vashishtha S, Efroni S, Nathanson L, Barnes Z, et al. 2013. Altered immune pathway activity under exercise challenge in Gulf War Illness: an exploratory analysis. *Brain, Behavior, and Immunity, 28*, 159-169.

Broderick G, Kreitz A, Fuite J, Fletcher MA, Vernon SD, and Klimas N. 2011. A pilot study of immune network remodeling under challenge in Gulf War Illness. *Brain, Behavior and Immunity, 25*(2), 302-313.

Bunegin L, Mitzel HC, Miller CS, Gelineau JF, and Tolstykh GP. 2001. Cognitive performance and cerebrohemodynamics associated with the Persian Gulf Syndrome. *Toxicology and Industrial Health, 17*(4), 128-137.

Calley CS, Kraut MA, Spence JS, Briggs RW, Haley RW, and Hart J Jr. 2010. The neuroanatomic correlates of semantic memory deficits in patients with Gulf War illnesses: a pilot study. *Brain Imaging and Behavior, 4*(1), 248-255.

Chao LL, Abadjian L, Hlavin J, Meyerhoff DJ, and Weiner MW. 2011. Effects of low-level sarin and cyclosarin exposure and Gulf War Illness on brain structure and function: a study at 4T. *Neurotoxicology, 32*(6), 814-822.

Chao LL, Kriger S, Buckley S, Ng P, and Mueller SG. 2014. Effects of low-level sarin and cyclosarin exposure on hippocampal subfields in Gulf War Veterans. *Neurotoxicology, 44*, 263-269.

Chao LL, Rothlind JC, Cardenas VA, Meyerhoff DJ, and Weiner MW. 2010. Effects of low-level exposure to sarin and cyclosarin during the 1991 Gulf War on brain function and brain structure in US veterans. *Neurotoxicology, 31*(5), 493-501.

Chao LL, Zhang Y, and Buckley S. 2015. Effects of low-level sarin and cyclosarin exposure on white matter integrity in Gulf War Veterans. *Neurotoxicology, 48*, 239-248.

Conboy L, St John M, and Schnyer R. 2012. The effectiveness of acupuncture in the treatment of Gulf War Illness. *Contemporary Clinical Trials, 33*, 557-562.

Cooper BY, Johnson RD, and Nutter TJ. 2016. Exposure to Gulf War Illness chemicals induces functional muscarinic receptor maladaptations in muscle nociceptors. *Neurotoxicology, 54*, 99-110.

Craddock TJ, Fritsch P, Rice MA Jr, del Rosario RM, Miller DB, Fletcher MA, et al. 2014. A role for homeostatic drive in the perpetuation of complex chronic illness: Gulf War Illness and chronic fatigue syndrome. *PLoS One, 9*(1), e84839.

Donta, ST, Clauw DJ, Engel CC Jr, Guarino P, Peduzzi P, Williams DA, et al. 2003. Cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: a randomized controlled trial. *Journal of the American Medical Association, 289*(11), 1396-1404.

Donta, ST, Engel CC Jr, Collins JF, Baseman JB, Dever LL, Taylor T, et al. (2004). Benefits and harms of doxycycline treatment for Gulf War veterans' illnesses: a randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine, 141*(2), 85-94.

Fukuda K, Nisenbaum R, Stewart G, Thompson WW, Robin L, Washko RM, et al. 1998. Chronic multisymptom illness affecting Air Force veterans of the GulfWar. *Journal of the American Medical Association, 280*(11), 981-988.

Golier JA, Caramanica K, Michaelides AC, Makotkine I, Schmeidler J, Harvey PD, et al. 2016. A randomized, double-blind, placebo-controlled, crossover trial of mifepristone in Gulf War veterans with chronic multisymptom illness. *Psychoneuroendocrinology, 54*, 22-30.

Golier, JA, Schmeidler J, Legge J, and Yehuda R. 2007. Twentyfour hour plasma cortisol and adrenocorticotropic hormone in Gulf War veterans: relationships to posttraumatic stress disorder and health symptoms. *Biological Psychiatry, 62*(10).

Golier JA, Schmeidler J, and Yehuda R. 2009. Pituitary response to metyrapone in Gulf War veterans: relationship to deployment, PTSD and unexplained health symptoms. *Psychoneuroendocrinology, 34*(9), 1338-1345.

Golomb BA, Allison M, Koperski S, Koslik HJ, Devaraj S, and Ritchie JB. 2014. Coenzyme Q10 benefits symptoms in Gulf War veterans: results of a randomized double-blind study. *Neural Computation*, *26*(11), 2549-2651.

Gopinath K, Gandhi P, Goyal A, Jiang L, Fang Y, Ouyang L, et al. 2012. FMRI reveals abnormal central processing of sensory and pain stimuli in ill Gulf War veterans. *Neurotoxicology, 33*(3), 261-271.

Grigoryan H, Li B, Anderson EK, Xue W, Nachon F, Lockridge O, et al. 2009. Covalent binding of the organophosphorus agent FP-biotin to tyrosine in eight proteins that have no active site serine. *Chemico-Biological Interactions, 180*(3), 492-498.

Grigoryan H, Schopfer LM, Thompson CM, Terry AV, Masson P, and Lockridge O. 2008. Mass spectrometry identifies covalent binding of soman, sarin, chlorpyrifos oxon, diisopropyl fluorophosphate, and FP-biotin to tyrosines on tubulin: a potential mechanism of long term toxicity by organophosphorus agents. *Chemico-biological interactions, 175*(1-3), 180-186.

Haley RW, Kurt TL, and Hom J. 1997. Is there a Gulf War Syndrome? Searching for syndromes by factor analysis of symptoms. *Journal of the American Medical Association, 277*(3), 215-222.

Haley RW, Luk GD, and Petty F. 2001. Use of structural equation modeling to test the construct validity of a case definition of Gulf War syndrome: Invariance over developmental and validation samples, service branches and publicity. *Psychiatry Research, 102*(2), 175-200.

Haley RW, Vongpatanasin W, Wolfe GI, Bryan WW, Armitage R, Hoffmann RF, et al. 2004. Blunted circadian variation in autonomic regulation of sinus node function in veterans with Gulf War syndrome. *American Journal of Medicine, 117*(7), 469-478.

Hattiangady B, Mishra V, Kodali M, Shuai B, Rao X, and Shetty AK. 2014. Object location and object recognition memory impairments, motivation deficits and depression in a model of Gulf War illness. *Frontiers in Behavioral Neuroscience, 8,* 78.

Hayer SD, Rabago DP, Amaza IP, Kille T, Coe CL, Zgierska A, et al. 2015. Effectiveness of nasal irrigation for chronic rhinosinusitis and fatigue in patients with Gulf War illness: Protocol for a randomized controlled trialOriginal. *Contemporary Clinical Trials, 41*, 219-226.

Hubbard N, Hutchison JL, Motes MA, Shokri-Kojori E, Bennett IJ, Brigante RM, et al. 2013. Central Executive Dysfunction and Deferred Prefrontal Processing in Veterans with Gulf War Illness. *Clinical Psychological Science, 2*(3), 319-327.

IOM, Institute of Medicine of the National Academies. 2014. *Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Reexamined.* Washington, D.C.: National Academies Press.

Jiang W, Duysen EG, Hansen H, Shlyakhtenko L, Schopfer LM, and Lockridge O. 2010. Mice treated with chlorpyrifos or chlorpyrifos oxon have organophosphorylated tubulin in the brain and disrupted microtubule structures, suggesting a role for tubulin in neurotoxicity associated with exposure to organophosphorus agents. *Toxicological Sciences, 115*(1), 183-193.

Klimas N. FY 2008. *The Use of Comprehensive Molecular Profiling with Network and Control Theory to Better Understand GWI and Model Therapeutic Strategies.* Congressionally Directed Medical Research Programs. W81XWH-09-2-0071

Koslik HJ, Hamilton G, and Golomb BA. 2014. Mitochondrial dysfunction in Gulf War illness revealed by ^{31}Phosphorus Magnetic Resonance Spectroscopy: a case-control study. *PLoS One, 9*(3), e9288.

Lange G, Tiersky LA, Scharer JB, Policastro T, Fiedler N, Morgan TE, et al. 2001. Cognitive functioning in Gulf War Illness. *Journal of Clinical and Experimental Neuropsychology, 23*(2), 240-249.

Middlemore-Risher ML, Adam BL, Lambert NA, and Terry AV Jr. 2011. Effects of chlorpyrifos and chlorpyrifos-oxon on the dynamics and movement of mitochondria in rat cortical neurons. *The Journal of Pharmacology and Experimental Therapeutics, 339*(2), 341-349.

Morris M. 2012. *Understanding Gulf War Illness: An Integrative Modeling Approach.* Congressionally Directed Medical Research Programs. W81XWH-13-2-0085

Nutter TJ, Johnson RD, and Cooper BY. 2105. A delayed chronic pain like condition with decreased Kv channel activity in a rat model of Gulf War Illness pain syndrome. *Neurotoxicology, 51*, 67-79.

O'Callaghan JP, Kelly KA, Locker AR, Miller DB, and Lasley SM. 2015. Corticosterone primes the neuroinflammatory response to DFP in mice: potential animal model of Gulf War illness. *133*(5), 708-721.

O'Callaghan JP, Sriram K, and Miller DB. 2008. Defining "neuroinflammation". *Annals of the New York Academy of Sciences, 1139*, 318-330.

Odegard TN, Cooper CM, Farris EA, Arduengo J, Bartlett J, and Haley R. 2013. Memory impairment exhibited by veterans with Gulf War Illness. *Neurocase, 19*(4), 316-327.

Ojo JO, Abdullah L, Evans J, Reed JM, Montague H, Mullan MJ, et al. 2014. Exposure to an organophosphate pesticide, individually or in combination with other Gulf War agents, impairs synaptic integrity and neuronal differentiation, and is accompanied by subtle microvascular injury in a mouse model of Gulf War agent exposure. *Neuropathology, 34*(2), 109-127.

Parihar VK, Hattiangady B, Shuai B, and Shetty AK. 2013. Mood and memory deficits in a model of Gulf War illness are linked with reduced neurogenesis, partial neuron loss, and mild inflammation in the hippocampus. *Neuropsychopharmacology, 38*(12), 2348-2362.

Pierce LM, Kurata WE, Matsumoto KW, Clark ME, and Farmer DM. 2016. Long-term epigenetic alterations in a rat model of Gulf War Illness. *Neurotoxicology, 55*, 20-35.

Proctor, SP, Heaton KJ, Heeren T, and White RF. (2006). Effects of sarin and cyclosarin exposure during the 1991 Gulf War on neurobehavioral functioning in US army veterans. *Neurotoxicology, 27*(6), 931-939.

RACGWI, Research Advisory Committe on Gulf War Veterans Illness. 2008. *Gulf War illness and the Health of Gulf War veterans: Scientific Findings and Recommendations.* Washington, D.C.: U.S. Government Printing Office.

RACGWVI, Research Advisory Committee on Gulf War Veterans' Illnesses. 2014. *Gulf War Illness and the Health of Gulf War Veterans: Research Update and Recommendations, 2009-2013.* Boston, MA: U.S. Government Printing Office.

Rayhan RU, Stevens BW, Raksit MP, Ripple JA, Timbol CR, Adewuyi O, et al. 2013a. Increased brain white matter axial diffusivity associated with fatigue, pain and hyperalgesia in Gulf War illness. *PLoS One, 8*(3), e58493.

Rayhan RU, Stevens BW, Timbol CR, Adewuyi O,Walitt B, VanMeter JW, et al. 2013b. Exercise challenge in Gulf War Illness reveals two subgroups with altered brain structure and function. *PLoS One, 8*(6), e63903.

Steele L. 2000. Prevalence and patterns of Gulf War illness in Kansas veterans: association of symptoms with characteristics of person, place, and time of military service. *American Journal of Epidemiology, 152*(10), 992-1002.

Storzbach D, Campbell KA, Binder LM, McCauley L, Anger WK, Rohlman DS et al. 2000. Psychological differences between veterans with and without Gulf War unexplained symptoms. Portland Environmental Hazards Research Center. *Psychosomatic Medicine, 62*(5), 726-735.

Storzbach D, Rohlman DS, Anger WK, Binder LM, and Campbell KA. 2001. Neurobehavioral deficits in Persian Gulf veterans: additional evidence from a population-based study. *Environmental Research, 85*(1), 1-13.

Sullivan K. 2012. *Brain Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC).* Congressionally Directed Medical Research Programs. W81XWH-13-2-0072

Sullivan K, Krengel M, Proctor SP, Devine S, Heeren T, and White RF. 2003. Cognitive functioning in treatment-seeking Gulf War Veterans: pyridostigmine bromide use and PTSD. *Journal of Psychopathology and Behavioral Assessment, 25*(9).

Toomey R, Alpern R, Vasterling JJ, Baker DG, Reda DJ, Lyons MJ, et al. 2009. Neuropsychological functioning of U.S. Gulf War veterans 10 years after the war. *Journal of the International Neuropsychological Society, 15*(5), 717-729.

Torres-Altoro MI, Mathur BN, Drerup JM, Thomas R, Lovinger DM, O’Callaghan JP, et al. 2011. Organophosphates dysregulate dopamine signaling, glutamatergic neurotransmission, and induce neuronal injury markers in striatum. *Journal of Neurochemistry, 119*(2), 303-313.

Wallin MT, Wilken J, Alfaro MH, Rogers C, Mahan C, Chapman JC, et al. 2009. Neuropsychologic assessment of a population-based sample of Gulf War veterans. *Cognitive and Behavioral Neurology, 22*(3), 155-166.

Whistler T, Fletcher MA, Lonergan W, Zeng XR, Lin JM, Laperriere A, et al. 2009. Impaired immune function in Gulf War Illness. *BioMed Central Medical Genomics, 2,* 12.

White RF, Proctor SP, Heeren T, Wolfe J, Krengel M, Vasterling J, et al. 2001. Neuropsychological function in Gulf War veterans: relationships to self-reported toxicant exposures. *Journal of Industrial Medicine, 40*(1), 42-54.

White RF, Steele L, O'Callaghan JP, Sullivan K, Binns JH, Golomb BA, et al. 2016. Recent research on Gulf War illness and other health problems in veterans of the 1991 Gulf War: Effects of toxicant exposures during deployment. *Cortex, 74*, 449-475.

Zakirova Z, Crynen G, Hassan S, Abdullah L, Horne L, Mathura V, et al. 2016. A Chronic Longitudinal Characterization of Neurobehavioral and Neuropathological Cognitive Impairment in a Mouse Model of Gulf War Agent Exposure. *Frontiers in Integrative Neuroscience, 9*, 71.

Zakirova Z, Tweed M, Crynen G, Reed J, Abdullah L, Nissanka N, et al. 2015. Gulf War agent exposure causes impairment of long-term memory formation and neuropathological changes in a mouse model of Gulf War Illness. *PLoS One, 10*(3), e0119579.